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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/101,132	06/30/98	TSUJI	S 760248P

002292 HM12/0121
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EXAMINER	
EPPS,J	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 01/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/101,132	Tsuji et al.
Examiner	**Group Art Unit**
Janet Epps	1635

☒ Responsive to communication(s) filed on *Oct 27, 1999*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *8-18* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☒ Claim(s) *8, 9, and 16-18* is/are allowed.

☒ Claim(s) *10-15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of References Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. Claims 1-7 have been canceled without prejudice or disclaimer. In the Office Action mailed 4/27/99, claims 1, 2 and 5-7 were examined and claims 3-4 were withdrawn from consideration pursuant to restriction of the claims. Newly added claims 8-18 are current pending on the instant application. The rejection of claims 1-2, and 5-7 are withdrawn in response to Applicant's cancellation of these claims, and arguments.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Response to Arguments

3. Applicant's arguments with respect to claims 1-2, and 5-7 have been considered but are moot in view of the cancellation of these claims and the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 12-14 read on an isolated nucleic acid sequence comprising an antisense oligonucleotide of at least 15 base pairs in length that hybridizes to a mRNA comprising the nucleotide sequence of SEQ ID NO. 1, but wherein thymidine residues are replaced by uridine residues, so as to inhibit translation of said mRNA, further wherein said antisense oligonucleotides are from 15 to 50 nucleotides in length, and vectors comprising said antisense oligonucleotides. Since the only disclosed use of antisense oligonucleotides targeting SCA2 mRNA described in the specification reads on methods of treating a SCA2 patient, claims reciting functional antisense oligonucleotides targeting SCA2 mRNA are subject to an enablement requirement.

The specification as filed does not disclose any functional antisense oligonucleotides, wherein said antisense oligonucleotide successfully hybridizes to a region of SCA2 mRNA, *in vitro* or *in vivo*, wherein upon hybridization translation of said mRNA is inhibited. Although the prior art as well as the specification as filed teaches that an antisense oligonucleotide targeting an mRNA of known sequence may be isolated, it is well established in the art that there is a significant level of unpredictability regarding the behavior of antisense base compounds. According to Crooke (1998), states that "extrapolations from in vitro uptake

studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also describes several "non-antisense effects", for example phosphorothioate modified oligonucleotides tend to bind to many proteins, protein binding in general by oligonucleotides may influence cell uptake, distribution, metabolism and excretion. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable, and thus much experimentation is required to screen multiple antisense compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected

mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted mRNA molecules and their association with cellular proteins can render target sites totally unaccessible *in vivo*.

Branch and Crooke teach that the behavior of antisense based pharmaceuticals are unpredictable, therefore claims to antisense based compounds are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Claim 15 reads on a method for treatment of spinocerebellar ataxia comprising administering to a patient suffering from spinocerebellar ataxia the vector of claim 14, in an amount effective for providing a normal amount of SCA2 protein having from 15 to 25 glutamine residues between amino acids 150 and 172.

The specification as filed does not provide sufficient guidance and/or any working examples describing methods of treatment of spinocerebellar ataxia comprising administering to a patient suffering from spinocerebellar ataxia a vector comprising a sequence encoding the SCA2 protein, the specification as filed does not provide sufficient instruction, guidance and/or description describing this gene therapy technique wherein the SCA2 protein is expressed in a subject in a sufficient amount wherein are treatment is effective in alleviating symptoms of spinocerebellar ataxia.

In regards to the level of unpredictability in the gene therapy art , Anderson (1998) states that "Gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease. Several major deficiencies still

exist including poor delivery systems, both viral and no-viral, and poor gene expression after genes are delivered." Furthermore, Orkin et al. (1995) state that " Daunting hurdles must be overcome if gene correction strategies are to achieve a meaningful clinical outcome.....Although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans." In addition, **In re Wands**, 858 F.d. 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations in determining whether or not undue experimentation would be involved in practicing inventions. These factors are: the quantity of experimentation necessary, the amount of direction or guidance needed, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims. The amount of experimentation necessary to determine the appropriate delivery system of compositions for gene therapy to the correct tissues, and to determine a means to regulate the level of gene expression once the composition has reached its target, which will be sufficient to correct the condition to be treated is beyond the scope of one with skill in the art. In view of the lack of guidance provided in the specification of the instant application, the unpredictability in the art regarding gene therapy techniques, and the breadth of the given claims, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 10-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Rabinovitch.

Rabinovitch teaches human chromosome libraries from chromosomes 8-12. Since the SCA2 locus is located on human chromosome 12, as ~~taught~~ evidenced by Pulst et al. (PTO-1449), the human chromosome library comprising the DNA of chromosome 12, isolated by Rabinovitch, would inherently hybridize to the nucleotide sequence of SEQ ID NO: 1 which corresponds to the coding sequence of the SCA2 gene.

Rabinovitch teaches each and every aspect of the instant invention thereby anticipating applicants' claimed invention.

Conclusion

8. Claims 8-9, and 16-18 are free of the prior art.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600

January 11, 2000